Kinetics and Mechanistic Approach to the Oxidative Behavior of Biological Anticancer Platinum(IV) Complex toward L-Asparagine in Acid Medium and the Effect of Copper(II) Catalyst

AHMED FAWZY[1,2]

[1] *Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516, Egypt*

[2] *Chemistry Department, Faculty of Applied Sciences, Umm Al-Qura University, Makkah Al-Mukarramah, 13401, Saudi Arabia Kingdom*

Received 25 April 2014; revised 4 October 2014; accepted 4 October 2014

DOI 10.1002/kin.20886

ABSTRACT: The catalytic effect of copper(II) ions toward the oxidation of L-asparagine (Asn) by an anticancer platinum(IV) complex in the form of hexachloroplatinate(IV) (HCP) has been investigated in aqueous acid medium at the constant ionic strength and temperature. The progress of both uncatalyzed and copper(II)-catalyzed oxidation reactions has been monitored spectrophotometrically. The stoichiometry in both cases is [Asn]/[HCP] = 1:1. The kinetics of both redox reactions is first order with respect to [oxidant] and less than the unit order in [acid]. The order with respect to $[\mathrm{Asn}]_T$ decreases from unity in the uncatalyzed path to less than unity in the catalyzed one. The catalyzed path is first order in $[\mathrm{Cu^{II}}]_T$. Increasing ionic strength and dielectric constant decreases the oxidation rates. The final oxidation products of L-asparagine are identified as the corresponding aldehyde (α-formyl acetamide), ammonium ion, and carbon dioxide. Tentative mechanisms of both reactions have been suggested. The

---

Correspondence to: A. Fawzy; e-mail: afsaad13@yahoo.com.

appropriate rate laws are deduced. The activation parameters of the uncatalyzed reaction have been evaluated and discussed. © 2014 Wiley Periodicals, Inc. Int J Chem Kinet 47: 1–12, 2015

INTRODUCTION

Oxidation reactions are of fundamental importance in nature and are regarded as key transformations in organic synthesis. Kinetic investigations on the homogeneous catalyzed oxidation of organic compounds in a liquid phase are considerably limited, and, therefore, the mechanistic exposition of such reactions has valuable contribution to the knowledge of chemistry.

The study of amino acids is one of the most exciting fields of organic chemistry. They play a significant role in a number of metabolic reactions such as biosynthesis of polypeptide, protein, and nucleotides. Thus the mechanism of analogous nonenzymatic chemical processes in the oxidation of amino acids is a potential area for intensive investigation [1] to understand some aspects of enzyme kinetics. The oxidation of α-amino acids is of great importance both from chemical point of view and its bearing on the mechanism of amino acids metabolism. They have been oxidized by a variety of reagents under different experimental conditions, and they often undergo oxidative decarboxylation and deamination [2–8].

L-Asparagine is one of the amino acids that occur in relatively high concentrations in plant tissues. Its role in the metabolism is crucial. It finds extensive applications in the production of pharmaceuticals and medicine, and as a reducing agent in chemical and biochemical systems. The rate of reduction by L-asparagine depends on the oxidant nature and pH of the medium. The oxidation of L-asparagine has been previously studied by few reagents such as sodium *N*-chloro-*p*-toluene sulfonamide catalyzed by Cu^{II} in alkaline media [4], alkaline diperiodatonickelate(IV) [5], peroxydisulfate in acid medium [6], and permanganate in acid [7] and alkaline [8] media. In most cases, the final oxidation products of L-asparagine were α-formyl acetamide, ammonia, and carbon dioxide.

Many metal ions in their complex form act as good oxidants in acidic, basic, and neutral media. However, oxidation capacity depends on their redox potential, and the latter depends on pH of the medium. There has been significant interest in the chemistry of biologically active platinum(IV) complexes for their remarkable anticancer properties [9–11]. Octahedral platinum(IV) complexes appeared attractive because they are usually substitution inert and require reduction to Pt^{II} species to act as potential anticancer drugs. The anticancer activity of platinum(IV) complexes is likely to be due to effective Pt^{IV} transport into the cell, followed by reduction to the more reactive platinum(II) compounds. Studies of oxidation of inorganic and organic substrates using platinum(IV) complexes in the form of hexachloroplatinate(IV) (HCP), $[PtCl_6]^{2-}$, as an oxidant are scarce and limited to a few cases [12–19], in which $[PtCl_6]^{2-}$ may behave as one- or two-electron oxidant, depending on the substrate and experimental conditions. The knowledge of the reactivity of platinum(IV) compounds toward their reduction by a potential bioreductant like L-asparagine may be important for understanding the mechanism of where antitumor activity as well as for designing new compounds with the least side effect. Chois et al. [19] reported that there is a correlation between a rate of reduction and anticancer activity in a series of homologous platinum(IV) complexes without going into the details of the reaction mechanism.

Transition metal ions have been widely employed as homogeneous catalysts for oxidation of organic and inorganic substrates by one of different paths such as formation of complexes with the reactants, oxidation of substrate itself, or through the formation of free radicals [20]. Studies of the oxidation reactions of amino acids catalyzed by metal ions are an important field of chemistry due to the role played by metals in biological systems. Copper(II) complexes of amino acids present important pharmacological interest as several of them show a wide spectrum of effects, including anti-inflammatory, antiulcer, anticonvulsant, and even antitumoral activity [21,22]. In the pharmacological activity of certain copper complexes when compared with that of the free ligands, the complexes are usually more active than the parent ligands. Some copper(II) complexes with L-asparagine have been reported in earlier studies [23–25].

An extensive literature survey revealed no report on the mechanistic studies of oxidation of L-asparagine by hexachloroplatinate(IV) in acid medium. Hence, we felt it would be worthwhile to investigate the oxidative behavior of hexachloroplatinate(IV) with L-asparagine in the absence and presence of copper(II) catalyst to explore the kinetic and mechanistic aspects of such redox reactions in strong acid medium. This study will enable to understand the complicated biological reaction in living systems and will also help to understand the catalytic activity of Cu^{II} along with the oxidative capacity of hexachloroplatinate(IV). In view of the above-mentioned arguments and the dearth of literature on the oxidation of this amino acid, I have carried out a detailed study of the title reaction.

EXPERIMENTAL

Materials and Methods

Materials. All chemicals employed in the present work were of reagent grade, and their solutions were prepared by dissolving the requisite amounts of the samples in doubly distilled water. A stock solution of L-asparagine (Asn; E. Merck, Germany) was prepared afresh by dissolving the amino acid sample in bidistilled water. Chloroplatinic acid solution (Johnson Matthey, USA) was used without further purification. Required solution of the reagent was freshly prepared before each experiment by proper dilution of its original solution, which was standardized spectrophotometrically [26]. The solution was stored in a dark bottle to keep away from light and restandardized periodically. The ionic strength, I, of the reaction mixtures was adjusted to 2.0 mol dm^{-3} using Na_2SO_4. The reactions temperature (25°C) was controlled within ±0.1°C.

Kinetic Measurements. The kinetic runs were followed under pseudo–first-order conditions with L-asparagine in at least a ten-fold excess over that of hexachloroplatinate(IV) at 25°C unless stated otherwise. The reactions were initiated by mixing the previously thermostated solutions of hexachloroplatinate(IV) and L-asparagine that also contained the calculated amount of H_2SO_4 and Na_2SO_4 to maintain the required acidity and ionic strength, respectively, and a copper(II) catalyst in the case of a catalyzed reaction. The courses of the reactions were followed by recording the decrease in absorbance, as a function of time, of hexachloroplatinate(IV) at its absorption maximum (262 nm), where hexachloroplatinate(IV) absorbs to a considerably greater extent than any of the other reactants and products, in a thermostated quartz cell on a Shimadzu UV-1800 PC automatic scanning double-beam spectrophotometer. The applicability of Beer's law was verified at 262 nm under the reaction conditions that the molar extinction coefficient, ε, was determined ($\varepsilon = 1.32 \pm 0.03 \times 10^4$ dm^3 mol^{-1} cm^{-1}) and was found to be in a good agreement with that reported previously [26]. Also, there was no interference from other reagents at this wavelength.

The reactions were followed for more than three half-lives. As the reduction of hexachloroplatinate(IV) by L-asparagine in acid medium proceeds with a measurable rate in the absence of copper(II) ions, the catalyzed reaction is understood to occur in parallel paths, with contributions from both the catalyzed and uncatalyzed paths. Thus, the total rate constant (k_T) is equal to the sum of the rate constants of the catalyzed (k_C) and uncatalyzed (k_U) reactions, so $k_C = k_T - k_U$. The pseudo–first-order rate constants (k_U and k_C) were determined from the slopes of the initial linear portions of ln(absorbance) versus time plots. The rate constants were the average of at least three independent kinetic runs and were reproducible to within ±4%.

The effect of dissolved oxygen on the reaction rates was checked by preparing the reaction mixtures and following the reactions under a nitrogen atmosphere. There are no significant changes in the results obtained in the presence of nitrogen from those in the presence of air.

RESULTS

Spectral Scans

The UV–vis spectral scans during the courses of the reactions between L-asparagine and hexachloroplatinate(IV) in the absence and presence of the copper(II) catalyst are shown in Figs. 1a and 1b, respectively. The spectrum of $[PtCl_6]^{2-}$ ions exhibits one absorption band with a maximum at $\lambda_{max} = 262$ nm. A gradual decrease in $[PtCl_6]^{2-}$ absorbance at its absorption maximum with time was observed without formation of new absorption bands, isosbestic points, or shifting λ_{max}.

Stoichiometry and Product Analysis

Different sets of reaction mixtures containing various amounts of hexachloroplatinate(IV) and L-asparagine at fixed acidity, ionic strength, and temperature were allowed to react for 24 h in an inert atmosphere. After completion of the reactions, the unreacted $[PtCl_6^{2-}]$ was assayed spectrophotometrically by measuring the absorbance at 262 nm, showing that 1 mol of $[PtCl_6]^{2-}$ consumed 1 mol of L-asparagine. The reaction stoichiometry may thus be represented as follows:

$$\begin{aligned} &H_2N(CO)CH_2 - CH(NH_2)COOH + [PtCl_6]^{2-} + H_2O \\ &= H_2N(CO)CH_2 - CHO + NH_4^+ + CO_2 \\ &\quad + [PtCl_4]^{2-} + 2Cl^- + H^+ \end{aligned} \tag{1}$$

The above stoichiometric equation is consistent with the results of products analysis. The products were identified as the corresponding aldehyde (α-formyl acetamide) by the spot test [27], the ammonium ion by

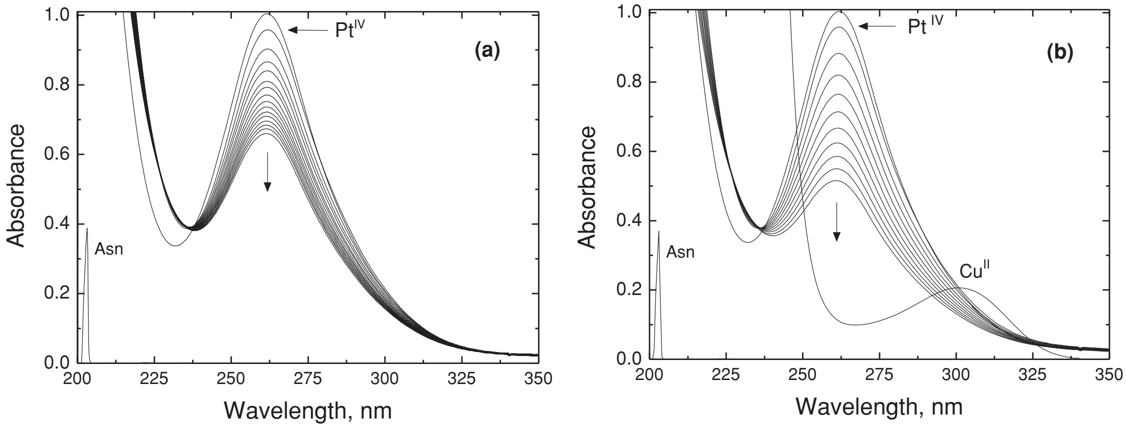


Figure 1 Spectral scans for (a) uncatalyzed and (b) copper(II)-catalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium. [Asn] = 6×10^{-2}, [$PtCl_6^{2-}$] = 7.6×10^{-5}, [H^+] = 1.0 and I = 2.0 mol dm^{-3} at 25°C. Scanning time intervals = 2 min. [Cu^{II}] = 5×10^{-4} mol dm^{-3}.

Nessler's reagent [28], and carbon dioxide by limewater. The product α-formyl acetamide was also estimated quantitatively as its 2,4-Dinitrophenylhydrazine derivative [28]. It was further observed that the aldehyde does not undergo further oxidation under the present experimental conditions, where a test for the corresponding carboxylic acid was negative. Similar oxidation products with different experimental conditions have also been reported earlier [4–8]. On the other hand, the formation of $[PtCl_4]^{2-}$ was confirmed [29] by the observed black precipitate of platinum(II) hydroxide on the addition of alkali to the reaction mixture, according to the following reaction:

$$[PtCl_4]^{2-} + 2OH^- = Pt(OH)_2 + 4Cl^-$$

Furthermore, a similar product was reported by others [29,30] for the reaction between $[PtCl_6]^{2-}$ and different reductants.

Reaction Order

The reaction orders (n) with respect to the reactants for both uncatalyzed and catalyzed reactions were determined from the slopes of the log k_U and log k_C versus log (concentration) plots using the relationship (log k = n log C + constant) by varying the concentrations (C) of substrate, acid, and catalyst, in turn, while keeping other conditions constant.

The oxidant, hexachloroplatinate(IV), was varied in the range from 4×10^{-5} to 12×10^{-5} mol dm^{-3} while keeping other conditions constant. It has been observed that the increase in the oxidant concentration does not alter the oxidation rate of L-asparagine (Table I). This indicates that the rate of oxidation is independent of the oxidant concentration and the order of reaction with respect to the oxidant is confirmed to be one.

Table I Influence of [$PtCl_6^{2-}$], [Asn], [H^+], and Ionic Strength, I, on the Pseudo–First-Order Rate Constant Values in the Uncatalyzed Oxidation of l-Asparagine by Hexachloroplatinate(IV) in Sulfuric Acid Medium at 25°C.

$\times 10^5$ [$PtCl_6^{2-}$] (mol dm^{-3})	$\times 10^2$ [Asn] (mol dm^{-3})	[H^+] (mol dm^{-3})	I (mol dm^{-3})	$\times 10^5$ k_U (s^{-1})
4.0	6.0	1.0	2.0	27.3
6.0	6.0	1.0	2.0	27.8
7.6	6.0	1.0	2.0	28.0
10.0	6.0	1.0	2.0	29.1
12.0	6.0	1.0	2.0	28.2
7.6	2.0	1.0	2.0	10.2
7.6	4.0	1.0	2.0	18.1
7.6	6.0	1.0	2.0	28.0
7.6	8.0	1.0	2.0	34.4
7.6	10.0	1.0	2.0	43.0
7.6	6.0	0.2	2.0	9.8
7.6	6.0	0.5	2.0	17.1
7.6	6.0	1.0	2.0	28.0
7.6	6.0	1.5	2.0	42.9
7.6	6.0	2.0	2.0	55.7
7.6	6.0	1.0	2.0	28.0
7.6	6.0	1.0	2.5	25.2
7.6	6.0	1.0	3.0	22.5
7.6	6.0	1.0	3.5	20.3
7.6	6.0	1.0	4.0	19.5

Experimental error ±3%.

The observed pseudo–first-order rate constants (k_U and k_C) were determined at different initial

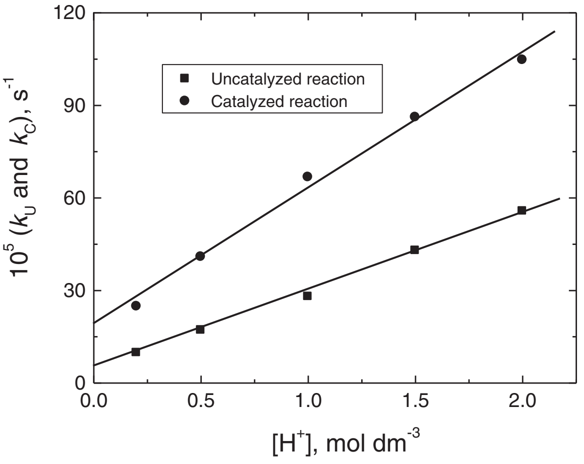


Figure 2 Plots of pseudo–first-order rate constants k_U and k_C versus [H^+] in the uncatalyzed and copper(II)-catalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium. [Asn] = 6×10^{-2}, [$PtCl_6^{2-}$] = 7.6×10^{-5}, and I = 2.0 mol dm^{-3} at 25°C. [Cu^{II}] = 5×10^{-4} mol dm^{-3}.

concentrations of the reductant L-asparagine, whereas other variables such as the concentration of the oxidant, copper(II) catalyst, and sodium sulfate were kept constant. The pH and temperature were also kept constant. Plots of the observed rate constants versus $[Asn]_T$ at the constant pH are linear, passing through origin for the uncatalyzed reaction and with a positive intercept for the catalyzed one. These observations confirm the first-order and fractional first-order ($n = 0.91$) dependences with respect to the amino acid for the uncatalyzed and catalyzed reactions, respectively.

Although the second-order rate constants were determined only at [H^+] = 1 mol dm^{-3}, the influence of pH was tested by measuring pseudo–first-order reaction rate coefficients at constant [Asn], [$PtCl_6^{2-}$], [Cu^{II}] (for the catalyzed reaction), ionic strength and temperature but with various [H^+] (0.2–2.0 mol dm^{-3}). The pseudo–first-order rate constants were found to increase with an increase in [H^+]. Plots of k_U and k_C versus [H^+] were linear with positive intercepts as shown in Fig. 2, confirming fractional first-order dependences with respect to [H^+].

Effect of Ionic Strength

To investigate the effect of the ionic strength on both catalyzed and uncatalyzed reactions, the reactions were studied at several initial concentrations of sodium sulfate but at constant concentrations of L-asparagine, $[PtCl_6]^{2-}$, and Cu^{II}, and at constant pH and temperature. The results are presented in Tables I and II. These results show that the pseudo–first-order rate constants (k_U and k_C) decrease with an increase in the ionic strength of the medium, and the Debye-Hückel plots were linear with negative slopes (Fig. 3).

Effect of the Dielectric Constant

The dielectric constant or the relative permittivity (D) effect was studied by varying the *t*-butyl alcohol–water content in the reaction mixtures at 25°C. The rate constants increase with the decrease in the dielectric constant of the solvent mixture. The plots of log k_U and log k_C versus $1/D$ were linear with positive slopes (figure not shown).

Effect of the [Cu^{II}] Catalyst

The reaction rate was measured with various [Cu^{II}], (3–8) $\times 10^{-4}$ mol dm^{-3}, while other variables remain constant. The reaction rate enhances with the increase in [Cu^{II}] (Table II). A plot of k_C versus [Cu^{II}] (Fig. 4) yielded a good linear plot passing through origin, suggesting that the order with respect to [Cu^{II}] is one as also confirmed from the plot of log k_C versus log[Cu^{II}] (slope $\approx$ 1).

Effect of Temperature

The influence of temperature on the rate of uncatalyzed reaction was studied at 20, 25, 30, and 35°C by keeping other variables constant. The observed rate constant k_U increases with raising of the temperature.

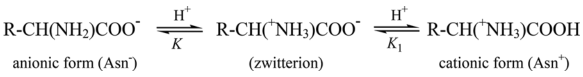
Polymerization Study

To study the possible presence of free radicals during the uncatalyzed and catalyzed reactions, the reaction mixtures to which a known amount of an acrylonitrile scavenger was initially added and was kept for 6 h in an inert atmosphere. On diluting the mixtures with methanol, no white precipitate was formed thus confirming the absence of free radical intervention in these reactions.

DISCUSSION

Nature of L-Asparagine in Acid Medium

Generally, amino acids are known [31] to exist in zwitterionic forms in equilibrium with anionic and cationic forms depending upon the pH of the solution according to the following equilibria:



$$\underset{\text{anionic form (Asn}^-)}{\text{R-CH(NH}_2\text{)COO}^-} \underset{K}{\overset{H^+}{\rightleftharpoons}} \underset{\text{(zwitterion)}}{\text{R-CH(}^+\text{NH}_3\text{)COO}^-} \underset{K_1}{\overset{H^+}{\rightleftharpoons}} \underset{\text{cationic form (Asn}^+)}{\text{R-CH(}^+\text{NH}_3\text{)COOH}}$$

Table II Influence of [$PtCl_6^{2-}$], [Asn], [H^+], [Cu^{II}], and Ionic Strength, I, on the Pseudo–First-Order Rate Constant in the Copper-Catalyzed Oxidation of l-Asparagine by Hexachloroplatinate(IV) in Sulfuric Acid Medium at 25°C.

$\times 10^5$ [$PtCl_6^{2-}$] (mol dm^{-3})	$\times 10^2$ [Asn] (mol dm^{-3})	[H^+] (mol dm^{-3})	$\times 10^4$ [Cu^{II}] (mol dm^{-3})	I (mol dm^{-3})	$\times 10^5$ k_C (s^{-1})
4.0	6.0	1.0	5.0	2.0	65.2
6.0	6.0	1.0	5.0	2.0	68.3
7.6	6.0	1.0	5.0	2.0	66.7
10.0	6.0	1.0	5.0	2.0	63.6
12.0	6.0	1.0	5.0	2.0	69.8
7.6	2.0	1.0	5.0	2.0	27.7
7.6	4.0	1.0	5.0	2.0	46.5
7.6	6.0	1.0	5.0	2.0	66.7
7.6	8.0	1.0	5.0	2.0	83.3
7.6	10.0	1.0	5.0	2.0	101.3
7.6	6.0	0.2	5.0	2.0	24.8
7.6	6.0	0.5	5.0	2.0	40.9
7.6	6.0	1.0	5.0	2.0	66.7
7.6	6.0	1.5	5.0	2.0	86.1
7.6	6.0	2.0	5.0	2.0	104.7
7.6	6.0	1.0	3.0	2.0	40.2
7.6	6.0	1.0	4.0	2.0	55.4
7.6	6.0	1.0	5.0	2.0	66.7
7.6	6.0	1.0	6.0	2.0	89.9
7.6	6.0	1.0	8.0	2.0	110.2
7.6	6.0	1.0	5.0	2.0	66.7
7.6	6.0	1.0	5.0	2.5	58.9
7.6	6.0	1.0	5.0	3.0	55.5
7.6	6.0	1.0	5.0	3.5	52.1
7.6	6.0	1.0	5.0	4.0	46.8

Experimental error ±4%.

where R is $H_2N(CO)CH_2$ and K_1 is the stepwise protonation constant of L-asparagine.

Because of the concentration of the hydrogen ion employed in the present reactions is sufficiently high as well as the observed enhancement of the reaction rates on increasing acid concentration, with a fractional first-order dependence on [H^+], the protonated form of L-asparagine (Asn^+) may be the reactive species in the rate-determining step, which plays the main role in the reaction kinetics.

Nature of Hexachloroplatinate(IV) Species

In acid medium, Kramer and Koch [32] reported that platinum(IV) species is present as $[PtCl_6]^{2-}$, which is assumed to be the principal reactive oxidant. The reduction of $[PtCl_6]^{2-}$ generally proceeds as follows:

$$[PtCl_6]^{2-} + 2e^- = [PtCl_4]^{2-} + 2Cl^-$$

In this redox process, octahedral Pt^{IV} is reduced to square planar Pt^{II} with release of two Cl^- ions. Therefore, this reaction is better classified as a reductive-elimination reaction [33]. The reduction potential of Pt^{IV}/Pt^{II} couple has been measured [34] as 0.68 V.

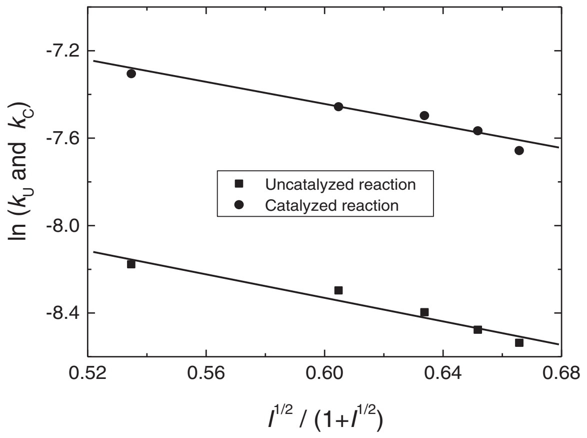


Figure 3 Debye–Hückel plots in the uncatalyzed and copper(II)-catalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium. [Asn] = 6 × 10^{-2}, [$PtCl_6^{2-}$] = 7.6 × 10^{-5}, and [H^+] = 1.0 mol dm^{-3} at 25°C. [Cu^{II}] = 5 × 10^{-4} mol dm^{-3}.

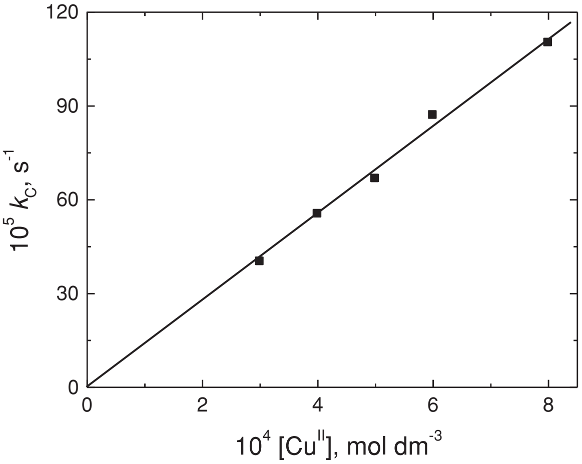


Figure 4 Plot of k_C versus $[Cu^{II}]$ in the copper(II)-catalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium. $[Asn] = 6 \times 10^{-2}$, $[PtCl_6^{2-}] = 7.6 \times 10^{-5}$, $[H^+] = 1.0$ and $I = 2.0$ mol dm^{-3} at 25°C.

Reaction Mechanism

Since platinum(IV) complexes are generally substitution inert [35], initial complex formation prior to electron transfer does not normally take place in reductive-elimination reactions [36] and electron transfer by a substitution controlled inner sphere mechanism is unlikely [35]. Halide-mediated reductive-elimination reactions of platinum(IV) complexes involving various inorganic [36] and biological [19,30] reductants have been suggested to take place via a nucleophilic attack by the reductant on a coordinated halide to a good leaving center, Pt^{IV} [30]. Reductive-elimination reactions of platinum(IV) compounds via a halide-bridged activated complex are formally equivalent to a transfer of Cl^+ from the oxidizing Pt^{IV} center to the reducing nucleophile, followed by loss of the trans ligand [37].

Two alternative reaction mechanisms for the oxidation of L-asparagine by hexachloroplatinate(IV) may be considered. The first mechanism involves a simultaneous two-electron transfer in a single step. The second one involves two successive one-electron transfer steps. If the transition states of reductant and/or oxidant are unstable, a simultaneous two-electron transfer mechanism may be suggested such as that in the oxidation of uranium(IV) by $[PtCl_6]^{2-}$ [38]. In the present study, addition of an acrylonitrile monomer to the reaction mixture failed to give polymerized products. It may be that the free radical like Pt^{III} species is too short-lived to interact with acrylonitrile to give the polymerized product under our experimental conditions. Consequently, the reaction can proceed either by a one-step two-electron mechanism or by a two successive one electron transfer mechanism.

Mechanism of Uncatalyzed Oxidation Reaction

The experimental data show that the pseudo–first-order rate constant for reduction of $[PtCl_6]^{2-}$ increases with decreasing pH with a fractional first-order dependence on $[H^+]$, suggesting that the amino acid substrate is first subjected to protonation (Eq. (2)).

The reaction between L-asparagine and $[PtCl_6]^{2-}$ has a stoichiometry of 1:1 with the first-order dependence on both $[PtCl_6]^{2-}$ and L-asparagine. The rate of reaction decreases on increasing the ionic strength and dielectric constant of the medium, suggesting that the reaction occurs between two ions with opposite charge [39,40].

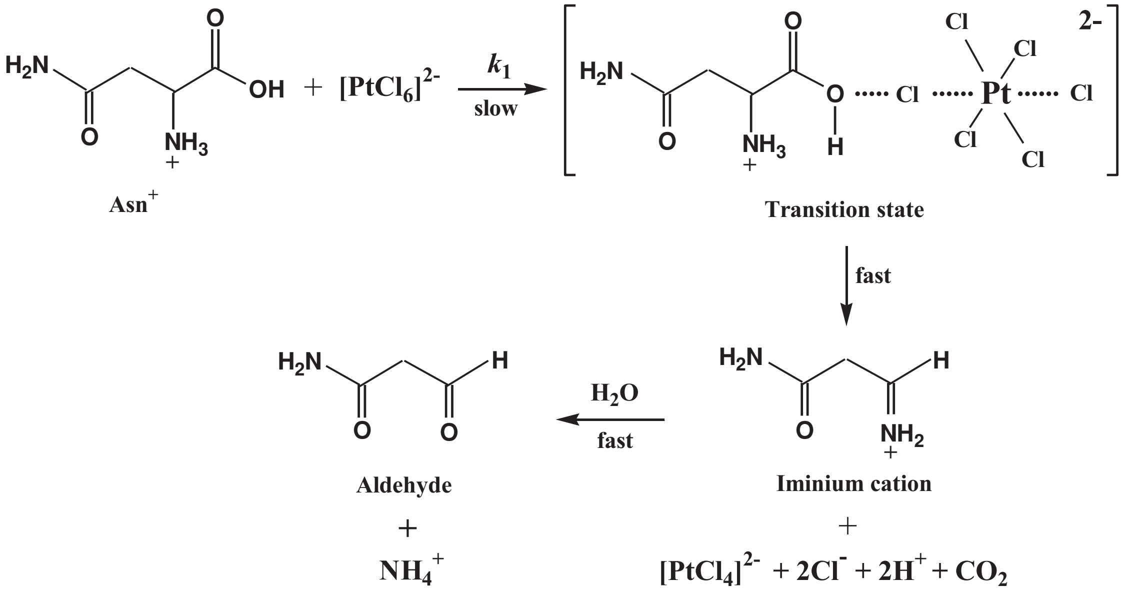
Initial complex formation between $[PtCl_6]^{2-}$ and L-asparagine can be excluded because of the substitution inertness of $[PtCl_6]^{2-}$. This is also confirmed by the absence of any spectroscopic evidence for the formation of such a complex in the UV–vis spectra as shown in Fig. 1a. Furthermore, the independence of [Asn] to the well–known Michaelis–Menten [41] kinetics, $1/k_U$ versus 1/[Asn], for enzyme-substrate reactions is considered as a kinetic evidence against intermediate formation.

A plausible mechanism for the redox process involves protonation of L-asparagine followed by an attack of the protonated amino acid on $[PtCl_6]^{2-}$ to give rise to the oxidation products as depicted by the following equations:

$$\mathrm{Asn} + \mathrm{H}^+ \overset{K_1}{\rightleftharpoons} \mathrm{Asn}^+ \tag{2}$$

$$\mathrm{Asn}^+ + [\mathrm{PtCl}_6]^{2-} \xrightarrow[\text{slow}]{k_1} \text{Products} \tag{3}$$

Within the protolytic L-asparagine system, there are carboxylate and amine groups, which may act as nucleophiles toward coordinated chloride, depending on pH of the medium [42]. The protolytic group with the highest basicity interacts with the platinum(IV) complex in the rate–determining step. Thus, at low pH, where the amine group is protonated, the carboxylate group should be able to attack $[PtCl_6]^{2-}$. When the carboxylate group approaches a chloride ligand in $[PtCl_6]^{2-}$, it forms a short–lived chloride–bridged transition state within which the electron density of the Pt^{IV}–chloride bond is displaced toward the platinum center, making the chloride ligand more prone to accept electrons from the incoming reductant nucleophile



Scheme 1 Mechanism of uncatalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium.

(L-asparagine) and transfer them to the platinum center rapidly (see Scheme 1). This facilitates the rapid reductive-elimination reaction. Therefore, such a reaction might be visualized as a nucleophilic substitution on the halogen with the platinum moiety as the leaving group. As already pointed out by Taube [43], no sharp distinction is visible between a two-electron redox change involving atom transfer and such a nucleophilic substitution. A concerted two-electron transfer from L-asparagine to the Pt^{IV} center leading to the release of two halide ions and formation of the reaction products is observed.

According to Eqs. (2) and (3), the redox reaction follows the second-order rate law as given by the following equation:

$$\text{Rate} = \frac{-d[\text{PtCl}_6^{2-}]}{dt} = \text{k}_1[\text{Asn}^+][\text{PtCl}_6^{2-}] = k_1K_1[\text{Asn}][\text{H}^+][\text{PtCl}_6^{2-}] \quad (4)$$

Under the pseudo–first-order condition, the rate law can be expressed by the following equation (5)

$$\text{Rate} = \frac{-d[\text{PtCl}_6^{2-}]}{dt} = k_\text{U}[\text{PtCl}_6^{2-}] \quad (5)$$

Comparing Eqs. (4) and (5), the following relationship is obtained:

$$k_\text{U} = k_1K_1[\text{Asn}][\text{H}^+] \quad (6)$$

where [Asn] is the equilibrium concentration of L-asparagine according to Eq. (2).

Thus the rate law expression becomes

$$k_\text{U} = \frac{k_1K_1[\text{H}^+]}{1 + K_1[\text{H}^+]}[\text{Asn}]_\text{T} = k'[\text{Asn}]_\text{T} \quad (7)$$

where $[\text{Asn}]_\text{T}$ is the total or stoichiometric concentration of L-asparagine ($[\text{Asn}]_\text{T} = [\text{Asn}] + [\text{Asn}^+]$) and k' is an empirical constant, which equals:

$$k' = \frac{k_1K_1[\text{H}^+]}{1 + K_1[\text{H}^+]} \quad (8)$$

Assuming that $K_1[\text{H}^+] >> 1$ [44,45], hence, Eq. (7) may be simplified to Eq. (9)

$$k_\text{U} = k_1[\text{Asn}]_\text{T} \quad (9)$$

According to Eq. (9), plots of k_U against $[\text{Asn}]_\text{T}$ at constant $[\text{H}^+]$ should be linear passing through origin as was experimentally observed at four temperatures (Fig. 5). The second-order rate constant obtained as slopes of such plots, along with its activation enthalpy and entropy, which are calculated from the Eyring plot (Fig. 6, are listed in Table III. The rate coefficient k_1 is expected to be dependent on pH because of the displacement of the protolytic equilibrium involving

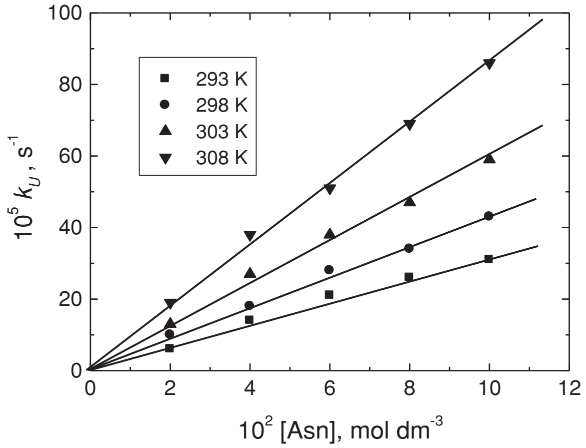


Figure 5 Plots of k_U versus [Asn] in the uncatalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium at different temperatures. $[PtCl_6^{2-}] = 7.6 \times 10^{-5}$, $[H^+] = 1.0$, and $I = 2.0$ mol dm^{-3}.

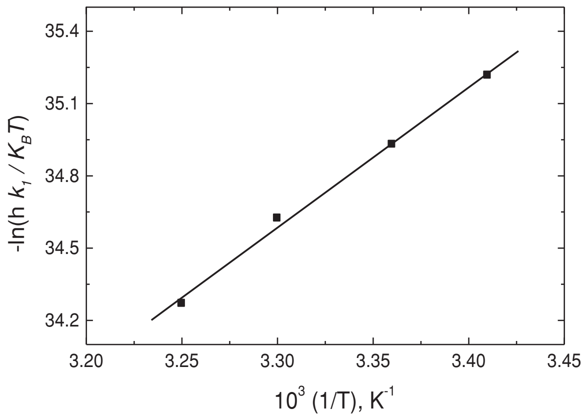


Figure 6 Eyring plot of the second-order rate constant in the uncatalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium. $[Asn] = 6 \times 10^{-2}$, $[PtCl_6^{2-}] = 7.6 \times 10^{-5}$, $[H^+] = 1.0$, and $I = 2.0$ mol dm^{-3} at 25°C.

Table III Activation Parameters of the Second-Order Rate Constant (k_1) in the Uncatalyzed Oxidation of l-Asparagine by Hexachloroplatinate(IV) in Sulfuric Acid Medium[a]

	Temperature (K)			
Parameter	293	298	303	308
$10^3 k_1$ ($dm^3\ mol^{-1}\ s^{-1}$)	3.12	4.21	5.83	8.40
$\Delta S^{\neq}$ (J $mol^{-1} K^{-1}$)			–152.81	
$\Delta H^{\neq}$ (kJ mol^{-1})			43.36	

[a] $[Asn] = 6 \times 10^{-2}$, $[PtCl_6^{2-}] = 7.6 \times 10^{-5}$, $[H^+] = 1.0$, and $I = 2.0$ mol dm^{-3}.

Experimental errors ±4%.

the cationic species of the amino acid (cf. Eq. (2)). The observed large negative value of $\Delta S^{\neq}$ suggests that the reactants form the transition state, which is more ordered than the reactants, due to loss of degrees of freedom. The experimental values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were both favorable for electron transfer processes.

Mechanism of Copper(II)-Catalyzed Reaction

The reaction between $[PtCl_6]^{2-}$ and L-asparagine in acid medium in the presence of small amounts of the copper(II) catalyst is similar to the uncatalyzed reaction with respect to stoichiometry, influence of the ionic strength and dielectric constant, and reaction orders, except for the order with respect to L-asparagine where addition of the Cu^{II} catalyst changed the order in [Asn] from unity to fractional. In addition, the reaction is first order with respect to the copper(II) catalyst.

The observed less than unit order in [Asn] presumably results from a complex formation between the catalyst copper(II) and substrate prior to the reaction with the oxidant. The formation of the complex was also proved kinetically by a nonzero intercept of the plot of $[Cu^{II}]/k_C$ versus 1/[Asn] (figure not shown). Such complexes between L-asparagine and copper(II) catalyst have been reported in earlier studies [25–27].

In view of the above-mentioned aspects, protonated L-asparagine is suggested to combine with Cu^{II} species, $[Cu(H_2O)_6]^{2+}$, to form an intermediate complex, $[Asn\text{–}Cu]^{3+}$, which then reacts in a slow step with 1 mol of $[PtCl_6]^{2-}$ to give rise to the products with regenerating the catalyst Cu^{II} (Scheme 2). The results are accommodated in the following sequence:

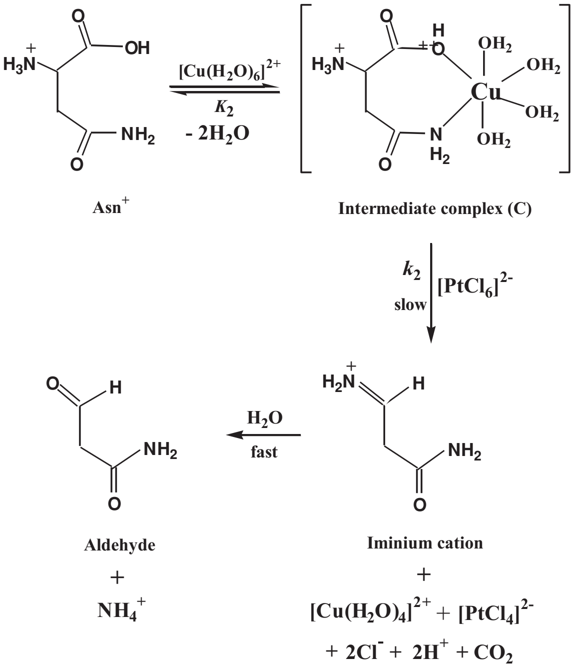
$$\mathrm{Asn} + \mathrm{H}^+ \overset{K_1}{\rightleftharpoons} \mathrm{Asn}^+ \tag{2}$$

$$\mathrm{Asn}^+ + \mathrm{Cu}^{2+} \overset{K_2}{\rightleftharpoons} [\mathrm{Asn} - \mathrm{Cu}]^{3+}(\mathrm{C}) \tag{10}$$

$$\mathrm{C} + [\mathrm{PtCl}_6]^{2-} \xrightarrow[\text{slow}]{k_2} \text{Products} + \mathrm{Cu}^{2+} \tag{11}$$

According to the proposed mechanism, the rate of disappearance of $[PtCl_6]^{2-}$ or formation of the products can be expressed by the following rate-law equation:

$$\text{Rate} = \frac{-d[\mathrm{PtCl}_6^{2-}]}{dt} = k_2[\mathrm{C}][\mathrm{PtCl}_6^{2-}] \tag{12}$$



Scheme 2 Mechanism of copper(II)-catalyzed oxidation of L-asparagine by hexachloroplatinate(IV) in sulfuric acid medium.

The relationship between the rate of complex formation and the substrate, hydrogen ion, catalyst, and oxidant concentrations can be deduced (see the Appendix) to give the following rate-law equation:

$$\text{Rate} = \frac{k_2 K_1 K_2[\text{Asn}][\text{H}^+][\text{Cu}^{\text{II}}][\text{PtCl}_6^{2-}]}{1 + K_1[\text{H}^+] + K_1 K_2[\text{Asn}][\text{H}^+] + K_1 K_2[\text{H}^+][\text{Cu}^{\text{II}}]} \quad (13)$$

In view of low concentration of $[\text{Cu}^{\text{II}}]$ used, the term $K_1K_2[\text{H}^+][\text{Cu}^{\text{II}}]$ in the denominator can be neglected. Therefore, Eq. (13) becomes

$$\text{Rate} = \frac{k_2 K_1 K_2[\text{Asn}][\text{H}^+][\text{Cu}^{\text{II}}][\text{PtCl}_6^{2-}]}{1 + K_1[\text{H}^+] + K_1 K_2[\text{Asn}][\text{H}^+]} \quad (14)$$

Under the pseudo–first-order condition,

$$\text{Rate} = \frac{-d[\text{PtCl}_6^{2-}]}{dt} = k_C[\text{PtCl}_6^{2-}] \quad (15)$$

Comparing Eqs. (14) and (15) and rearrangement, Eq. (16) is obtained:

$$\frac{[\text{Cu}^{\text{II}}]}{k_C} = \left(\frac{1 + K_1[\text{H}^+]}{k_2 K_1 K_2[\text{H}^+]}\right)\frac{1}{[\text{Asn}]} + \frac{1}{k_2} \quad (16)$$

According to Eq. (13), at constant $[\text{H}^+]$, the plot of $[\text{Cu}^{\text{II}}]/k_C$ against 1/[Asn] was found be linear with a positive intercept (figure not shown), supporting the Cu^{II}–asparagine complex. From the intercept of such plot, the value of the rate constant of the slow step (k_2) is calculated to be 0.33 $\text{dm}^3\ \text{mol}^{-1}\ \text{s}^{-1}$.

APPENDIX: DESCRIPTION

According to the suggested mechanism for copper(II)–catalyzed oxidation reaction,

$$\text{Rate}_{(C)} = \frac{-d[\text{PtCl}_6^{2-}]}{dt} = k_2[\text{C}][\text{PtCl}_6^{2-}] \quad (A1)$$

From Eq. (2)

$$K_1 = \frac{[\text{Asn}^+]}{[\text{Asn}][\text{H}^+]} \quad (A2)$$

Therefore,

$$[\text{Asn}^+] = K_1[\text{Asn}][\text{H}^+] \quad (A3)$$

From reaction (10) and Eq. (A3)

$$K_2 = \frac{[\text{C}]}{[\text{Asn}^+][\text{Cu}^{\text{II}}]} = \frac{[\text{C}]}{K_1[\text{Asn}][\text{H}^+][\text{Cu}^{\text{II}}]} \quad (A4)$$

$$\text{Therefore,}\ [\text{C}] = K_1 K_2[\text{Asn}][\text{H}^+][\text{Cu}^{\text{II}}] \quad (A5)$$

Substituting Eq. (A5) into Eq. (A1) yields

$$\text{Rate}_{(C)} = k_2 K_1 K_2[\text{Asn}][\text{H}^+][\text{Cu}^{\text{II}}][\text{PtCl}_6^{2-}] \quad (A6)$$

The total concentration of L-asparagine is given by

$$[\text{Asn}]_\text{T} = [\text{Asn}]_\text{F} + [\text{Asn}^+] + [\text{C}] \quad (A7)$$

where $[\text{Asn}]_\text{T}$ and $[\text{Asn}]_\text{F}$ stand for total and free concentrations of L-asparagine.

Substituting Eqs. (A3) and (A5) into Eq. (A7) gives

$$[\text{Asn}]_\text{T} = [\text{Asn}]_\text{F} + K_1[\text{Asn}]_\text{F}[\text{H}^+] + K_1 K_2[\text{Asn}]_\text{F}[\text{H}^+][\text{Cu}^{\text{II}}] \quad (A8)$$

$$[\text{Asn}]_\text{T} = [\text{Asn}]_\text{F}(1 + K_1[\text{H}^+] + K_1 K_2[\text{H}^+][\text{Cu}^{\text{II}}]) \quad (A9)$$

Therefore,

$$[\mathrm{Asn}]_\mathrm{F} = \frac{[\mathrm{Asn}]_\mathrm{T}}{1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{H}^+][\mathrm{Cu}^{\mathrm{II}}]} \quad \text{(A10)}$$

Similarly,

$$[\mathrm{Cu}^{\mathrm{II}}]_\mathrm{T} = [\mathrm{Cu}^{\mathrm{II}}]_\mathrm{F} + [\mathrm{C}] \quad \text{(A11)}$$

Substituting Eq. (A5) into Eq. (A11) and rearrangement gives

$$[\mathrm{Cu}^{\mathrm{II}}]_\mathrm{F} = \frac{[\mathrm{Cu}^{\mathrm{II}}]_\mathrm{T}}{1 + K_1K_2[\mathrm{Asn}][\mathrm{H}^+]} \quad \text{(A12)}$$

In view of the high concentrations of $[\mathrm{H}^+]$

$$[\mathrm{H}^+]_\mathrm{T} = [\mathrm{H}^+]_\mathrm{F} \quad \text{(A13)}$$

Also,

$$[\mathrm{PtCl}_6^{2-}]_\mathrm{T} = [\mathrm{PtCl}_6^{2-}]_\mathrm{F} \quad \text{(A14)}$$

Substituting Eqs. (A10), (A12), (A13), and (A14) into Eq. (A6) (and omitting T and F subscripts) gives

$$\mathrm{Rate}_{(\mathrm{C})} = \frac{k_2K_1K_2[\mathrm{Asn}][\mathrm{H}^+][\mathrm{Cu}^{\mathrm{II}}][\mathrm{PtCl}_6^{2-}]}{1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{Asn}][\mathrm{H}^+] + K_1K_2[\mathrm{H}^+][\mathrm{Cu}^{\mathrm{II}}]} \quad \text{(A15)}$$

In view of low concentration of $[\mathrm{Cu}^{\mathrm{II}}]$ used, the term K_1K_2 $[\mathrm{H}^+]$ $[\mathrm{Cu}^{\mathrm{II}}]$ in the denominator of Eq. (A15) can be neglected. Therefore, Eq (A15) becomes

$$\mathrm{Rate}_{(\mathrm{C})} = \frac{k_2K_1K_2[\mathrm{Asn}][\mathrm{H}^+][\mathrm{Cu}^{\mathrm{II}}][\mathrm{PtCl}_6^{2-}]}{1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{Asn}][\mathrm{H}^+]} \quad \text{(A16)}$$

Under pseudo–first-order conditions, the rate law can be expressed as

$$\mathrm{Rate}_{(\mathrm{C})} = \frac{-d[\mathrm{PtCl}_6^{2-}]}{dt} = k_\mathrm{C}[\mathrm{PtCl}_6^{2-}] \quad \text{(A17)}$$

Comparing Eqs. (A16) and (A17), the following relationship is obtained:

$$k_\mathrm{C} = \frac{k_2K_1K_2[\mathrm{Asn}][\mathrm{H}^+][\mathrm{Cu}^{\mathrm{II}}]}{1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{Asn}][\mathrm{H}^+]} \quad \text{(A18)}$$

and with rearrangement, it becomes

$$\frac{[\mathrm{Cu}^{\mathrm{II}}]}{k_C} = \left(\frac{1 + K_1[\mathrm{H}^+]}{k_2K_1K_2[\mathrm{H}^+]}\right)\frac{1}{[\mathrm{Asn}]} + \frac{1}{k_2} \quad \text{(A19)}$$

BIBLIOGRAPHY

1. Hemmige, S. Y.; Chapuradoddi, R. R.; Kikkeri, N. M. Turk J Chem 2003, 27, 571–580.
2. Goel, A.; Sharma, S. Trans Met Chem 2010, 35, 549–554.
3. Jose, T. P.; Nandibewoor, S. T.; Tuwar, S. M. J Sol Chem 2006, 35, 51–62.
4. Senagar, S. K. S.; Yadav, B. S. J Indian Chem Soc 1988, 65, 88–90.
5. Sanjeevagowda, T. P.; Mahantesh, A. A.; Abdulazizkhan, L. H. J Sol Chem 2008, 37, 1795–180.
6. Khalid, M. A. A. J Sci Eng 2007, 33, 199–210.
7. Zahedi, M.; Bahrami, H. Kinet Catal 2004, 45, 351–358.
8. Fawzy, A.; Ashour, S. S.; Musleh, M. A. React Kinet Mech Catal 2014, 111, 443–460.
9. Lemma, K.; Shi, T.; Elding, L. I. Inorg Chem 2000, 39, 1728–1734.
10. Weiss, R. B.; Christian, M. C. Drugs 1993, 46, 360–377.
11. Keage, M. C.; Kelland, M. J.; Neidles, L. R.; Warning, M. J. (Eds). Molecular Aspects of Anticover Drug DNA Interactions, Vol. 1; CRC Press: New York, 1993.
12. Sen Gupta, K. K.; Sen, P. K.; Sen Gupta, S. Inorg Chem 1977, 16, 1396–1399.
13. Sen Gupta, K. K.; Sen, P. K. J Inorg Nucl Chem 1977, 39, 1651–1653.
14. Sen Gupta, K. K.; Das, S., Sen Gupta, S. Trans Met Chem 1988, 13, 55–159.
15. Pal, B.; Sen Gupta, K. K.; Bull Chem Soc Japan 2000, 73, 553–560.
16. Sen Gupta, K. K.; Begum, B. A.; Ghosh, S. P. Trans Met Chem 1998, 23, 295–299.
17. Sen Gupta, K. K.; Begum, B. A.; Pal, B. Carbohydr Res 1998, 309, 303–310.
18. Pal, B.; Sen Gupta, K. K.; Sen, P. K. Trans Met Chem 2005, 30, 593–600.
19. Choi, S.; Filotto, C.; Bisanzo, M.; Delaney, S.; Lagasee, D.; Whitworth, J. L.; Jusko, A.; Li, C., Wood, N. A.; Willingham, J.; Schwenker, A.; Spaulding, K. Inorg Chem 1988, 37, 2500–2504.
20. Shukla, A.; Gupta, S.; Upadhyay, S. K. Int J Chem Kinet 1991, 23, 279–288.
21. Sorenson, J. R. J Med Chem 1976, 19, 135–148.
22. Sorenson, J. R. J. In Metal Ions in Biological Systems, Vol. 14; Sigel, H., Ed.; Marcel Dekker: New York, 1982; p. 77.
23. Baran, E. J.; Viera, I.; Torre, M. H. Spectrochim Acta 2007, 66A, 114–117.
24. Lomozik, L.; Wojciechowska, A.; Jaskólski, M. Monatsh Chem 1983, 114, 1185–1188.

25. Methenitis, C.; Morcellet, J.; Pneumatikakis, G.; Morcellet, M. Macromolecules 1987, 20, 49–53.
26. Georgieva, M.; Andonovski, B. Anal Bioanal Chem 2003, 375, 836–839.
27. Feigl, F. Spot Tests in Organic Analysis; Elsevier: New York, 1975; p. 195.
28. Vogel, A. I. A Text Book of Practical Organic Chemistry, 3rd ed.; ELBS Longman: London, 1973; p. 27, 332.
29. Pal, B.; Sen Gupta, K. K. Trans Met Chem 2012, 37, 671–678.
30. Shi, T.; Berglund. J.; Elding. L. I. Inorg Chem 1996, 35, 3498–3503.
31. Martell, A. E.; Smith, R. M. In: Critical Stability Constants. Vol. I; Plenum Press: New York, 1974; p. 321.
32. Kramer, J.; Koch, K. R. Inorg Chem 2006, 45, 7843–7855.
33. Lemma, K.; Sargeson, A.; Elding, L. I. J Chem Soc, Dalton Trans 2000, 7, 1167–1172.
34. Latimer, W. M. Oxidation Potentials, 2nd ed.; Prentice-Hall: Upper Saddle River, NJ, 1961; p. 206.
35. Mason, W. R. Coord Chem Rev 1972, 7, 241–255.
36. Berglund, J.; Voigt, R.; Fronaeus, S.; Elding, L. I. Inorg Chem 1994, 33, 3346–3353.
37. Wilmarth, W. K.; Dooly, M. M.; Byrd, J. E. Coord Chem Rev 1983, 51, 125–133.
38. Hassan, R. M.; Kojima, T.; Fukutomi, H. In: International Symposium on Solute-Solute-Solvent Interactions, Japan, 1982; p 113.
39. Frost, A. A.; Person, R. G. Kinetics and Mechanism; Wiley Eastern: New Delhi, 1970; pp. 147–150.
40. Amis, E. S. Solvent Effect on Reaction Rates and Mechanism; Academic Press: New York, 1966; p. 28.
41. Michaelis, L.; Menten, M. L. Biochem Z 1913, 49, 333–369.
42. Shi, T.; Berglund. J.; Elding. L. I. J Chem Soc, Dalton Trans 1997, 2073–2077.
43. Taube, H.; Rorabacher, D. B.; Endicott, J. F. (Eds.). Mechanistic Aspects of Inorganic Reactions, ACS Symposium Series, Vol. 198; American Chemical Society: Washington, DC, 1982; pp. 151–199.
44. Rao, C. N.; Ramanaiah, M.; Sailaja, B. B. V. Res Paper 2014, 3, 23–26.
45. Teksoz, S.; Unak, P. Phys Chem Liq 2006, 42, 569–575.